REMARKS

This responds to the Office Action mailed on October 23, 2009.

Claims 184-185 are added; as a result, claims 153-154, 157-165, 174-176, and 181-186 are now pending in this application.

The Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 153-154, 157-165, 169[sic]-175, and 181-182 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194, 196-203, 205-211, and 231 of copending application Serial No. 09/754,775. As neither the present application nor the '775 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the '775 application.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,472,985. This rejection is respectfully traversed.

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct because the copending application [sic; patent] teaches an aspect of the claims in the instant application.

Claims 1-11 of the '985 patent are directed to a method for inhibiting pathological proliferation of mammalian smooth muscle cells which method comprises administering to a mammal at risk of a condition characterized by pathological proliferation of smooth muscle cells, the following: an amount of trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine, or a structural analog thereof effective to activate or stimulate production of TGF-beta, wherein the amount is administered over time to the mammal as a preventative measure, for a condition selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke; a method for inhibiting pathological proliferation of mammalian smooth muscle cells which method comprises administering to a mammal at risk of a condition characterized by pathological proliferation of smooth muscle cells, the following:

an amount of trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine, or a structural analog thereof effective to activate or stimulate production of TGF-beta, wherein the amount is administered over time to the mammal as a preventative measure, for a condition selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke; and a therapeutic method for inhibiting pathological proliferation of vascular smooth muscle cells associated with atherosclerosis, comprising systemically administering to a mammal afflicted with atherosclerosis, an amount of trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine or a structural analog thereof effective to elevate the level of active TGF-beta, to inhibit the pathological proliferation of said smooth muscle cells.

In contrast, claims 153-154, 159-160, 165, and 181-182 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevates TGF-beta.

The Examiner is respectfully reminded that it is only the claims of an issued patent, not the entire disclosure, that may be employed in support of an obviousness-type double patenting rejection. M.P.E.P. § 804(II)(B)(1). Moreover, all aspects of the claims must be considered not just "an aspect" in evaluating obviousness-type double patenting.

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '985 patent is respectfully requested.

Claims 174-175 and 183-184 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 11, 13, and 15 of U.S. Patent No. 5,599,844. This rejection is respectfully traversed.

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application [sic; patent] teaches an aspect of the claims in the instant application.

Claims 1, 9, 11, 13, and 15 in the '844 patent are directed to a therapeutic method to treat procedural vascular trauma, comprising orally administering to a mammal subjected to the vascular trauma an amount of an agent effective upon oral administration to elevate the level of TGF-beta so as to inhibit the pathological proliferation of vascular smooth muscle cells, and a method for reducing or inhibiting restenosis associated with an angioplasty procedure, which

method comprises orally administering to a mammal an amount of an agent effective upon oral administration to elevate levels of TGF-beta.

In contrast, claims 174-175 and 183-184 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevates TGF-beta.

The Examiner is respectfully reminded that it is only the claims of an issued patent, not the entire disclosure, that may be employed in support of an obviousness-type double patenting rejection. M.P.E.P. § 804(II)(B)(1). Moreover, all aspects of the claims must be considered not just "an aspect" in evaluating obviousness-type double patenting.

Therefore, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '844 patent is respectfully requested.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4 of U.S. Patent No. 5,773,479. This rejection is respectfully traversed.

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application [sic; patent] teaches an aspect of the claims in the instant application.

Claims 1-2 and 4 in the '479 patent are directed to a method to treat atherosclerosis comprising the systemic administration to a mammal of an amount of trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine or an analog thereof that is effective to inhibit or reduce lesion formation or development in, or lipid accumulation by, a vessel of said mammal, and a method of treating atherosclerosis comprising administering to a mammal an amount of trans-2[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine or an analog thereof that is effective to inhibit or reduce lesion formation or development in, or lipid accumulation by, a vessel of said mammal.

In contrast, claims 153-154, 159-160, 165, and 181-182 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta .

The Examiner is respectfully reminded that all aspects of the claims must be considered not just "an aspect" in evaluating obviousness-type double patenting.

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '479 patent is respectfully requested.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-5 and 9-11 of U.S. Patent No. 5,847,007. This rejection is respectfully traversed.

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application [sic; patent] teaches an aspect of the claims in the instant application.

Claims 1, 4-5 and 9-11 in the '007 patent are directed to a method for preventing atherosclerosis in a mammal at risk therefor, or treating atherosclerosis in a mammal, which method comprises orally administering to the mammal the following: a dose of a therapeutic agent in an amount effective when administered orally to elevate the level of TGF-beta, wherein the increase in TGF-beta inhibits atherosclerotic lesion formation or development in the mammal, and a therapeutic method comprising orally administering to a mammal an amount of a therapeutic agent effective upon oral administration to elevate the level of TGF-beta so as to treat a diseased blood vessel in said mammal, wherein said disease is associated with the diminution in the lumen volume of the diseased vessel, and wherein the therapeutic agent stabilizes atherosclerotic plaque, inhibits lipid accumulation, or inhibits or reduces diminution in vessel lumen diameter in the diseased vessel.

In contrast, claims 153-154, 159-160, 165, and 181-182 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevates TGF-beta.

The Examiner is respectfully reminded that all aspects of the claims must be considered not just "an aspect" in evaluating obviousness-type double patenting.

Therefore, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '007 patent is respectfully requested.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-10 of U.S. Patent No. 6,166,090. This rejection is respectfully traversed.

Claims 1 and 3-10 in the '090 patent are directed to a method for preventing atherosclerosis in a mammal at risk therefor, or treating atherosclerosis in a mammal, which method comprises systemically administering to the mammal an effective amount of a therapeutic agent to increase the level of TGF-beta, so as to inhibit atherosclerotic lesion formation or development in the mammal; a method for treating atherosclerosis in a mammal comprising administering to a mammal an effective amount of a therapeutic agent comprising trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine, or an analog thereof, wherein the therapeutic agent stabilizes atherosclerotic plaque; a method for treating atherosclerosis in a mammal comprising administering to a mammal an effective amount of an agent comprising trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine, or an analog thereof, wherein the therapeutic agent inhibits vessel lumen diminution associated with atherosclerosis; a method for treating atherosclerosis in a mammal comprising administering to a mammal an effective amount of a therapeutic agent comprising trans-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine, or an analog thereof; and a method for treating atherosclerosis in a mammal comprising administering to a mammal an effective amount of an analog of trans-2- [4-(1 ,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethylamine.

In contrast, claims 153-154, 159-160, 165, and 181-182 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta.

Hence, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '090 patent is respectfully requested.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 19, 27, 30-39, and 41-42 of U.S. Patent No. 6,251,920. This rejection is respectfully traversed.

Claims 1, 10, 19, 27, 30-39, and 41-42 in the '920 patent are directed to a therapeutic method for treating a condition selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction and stroke, comprising administering to a mammal afflicted with said condition, an effective amount of a compound of formula (I); a method comprising administering to a mammal at risk of a cardiovascular condition the following: an effective amount of a compound of formula (I), wherein the amount is administered over time to the mammal to prevent a cardiovascular condition selected from the group consisting of thrombosis, myocardial infarction, and stroke; therapeutic method for preventing atherosclerosis, comprising systemically administering to a mammal afflicted with atherosclerosis, an effective amount of a compound of formula (I); and a therapeutic method for preventing or treating a cardiovascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said cardiovascular indication, a cytostatic dose of a therapeutic agent, wherein the cytostatic dose is effective to increase the level of TGF-beta so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, plaque stability, or any combination thereof.

In contrast, claims 153-154, 159-160, 165, and 181-182 in the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta.

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '920 patent is respectfully requested.

Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 6,262,079. This rejection is respectfully traversed.

Claim 17 of the '079 patent is directed to a therapeutic method comprising inhibiting vascular smooth muscle cell proliferation comprising administering to a mammal an effective cytostatic antiproliferative amount of a compound selected from the group consisting of tamoxifen, a tamoxifen analog, a pharmaceutically acceptable salt of tamoxifen, and a pharmaceutically acceptable salt of a tamoxifen analog, wherein the administration is by placement of a vascular shunt or intravascular stent comprising the compound.

In contrast, independent claims 153-154 and 181-182 of the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta.

Hence, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '079 patent is respectfully requested.

The 35 U.S.C. § 112 Rejections

Claims 153-154, 157-165 and 174-176 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (a "new matter" rejection). This rejection is respectfully traversed.

The Examiner asserts that although the specification has support for "increasing plaque stability," it does not provide support for "inhibit plaque."

On page 17 of the specification, it is disclosed that

> agents, which increase the level of TGF-beta, [are] used in early therapeutic intervention for reducing, delaying, or eliminating (and even reversing) atherosclerotic plaque formation and areas of vascular wall hypertrophy and/or hyperplasia (emphasis added).

It is also disclosed that smooth muscle cells (SMC) and monocyte/macrophage inflammatory cells in the intima of the vessel wall take up lipid to form a mature atherosclerotic lesion (page 2 of the specification). The specification discloses that the formation of an atherosclerotic lesion can occur in five stages, which include migration of SMC into an enlarged intima, and lipid accumulation and storage by intimal SMC (pages 41-42 of the specification). It is further disclosed that the accumulation of lipid is necessary for the progression of the lesion to clinical significance, and that inhibition of lipid accumulation in the SMC should significantly reduce or prevent lesion formation and/or progression, thus reducing or preventing atherosclerosis and resultant myocardial infarction, recruitment of inflammatory cells to in the lesion, and possibly proliferation in lesions (page 42 of the specification). It is disclosed that the ultimate effect that inhibition of apo(a) has on atherosclerosis is dependent on the contribution of SMC proliferation to initiation or progression of an atherosclerotic plaque (page 42 of the specification).

Therefore, the specification supports the use of an agent that inhibits plaque (atherosclerotic lesion) formation or development.

Withdrawal of the § 112, first paragraph, "new matter" rejection is respectfully requested.

Claims 153-154, 157-165 and 169-184 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. This rejection is respectfully traversed.

In particular, the Examiner asserts that because the specification does not teach administration of any of the claimed compounds in treating any of the cardiovascular indications in mammals as listed in the claims, and because the compounds have different biological activities, bioavailabilities, pharmacokinetic profiles, and pharmacological efficacy, the specification does not reasonably provide enablement for a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter.

It is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of the invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Thus, the fact that a compound falling within the scope of the claims that elevates TGF-beta levels would have to be determined or selected, and a cytostatic dose selected or administered does not constitute "undue experimentation," particularly in an art where the level of skill is high. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

With regard to evidence that agents within the scope of the claims are useful, please consider that idoxifene and toremifene have been shown to have beneficial cardiovascular effects (see Example 6 and the abstracts for Yue et al., Circ., 102:III281 (2000), Erkkola et al., Breast Can. Res. Treat., 93:277 (2005), Harvey et al., Breast, 15:142 (2005), Kusama et al., Breast Can. Res. Treat., 88:9 (2004), Kusama et al., Breast Can. Res. Treat., 88:1 (2004), Christopher et al., Eur. J. Pharmacol., 446:139 (2002), and Johnston et al., Cancer Chemo. Pharmacol., 53:341 (2004); a copy of each is enclosed herewith).

Regardless of whether tamoxifen, hexesterol or clomiphene (a stilbene type antisteroid) have adverse side effects (most approved drugs have one or more adverse side effects), the

claims are directed to selecting agents from certain classes of agents and administering a cytostatic amount of that agent. The specification discloses methods to determine agents that elevate TGF-beta levels and it is Applicant's position that it is within the skill of the art to select and administer appropriate dosages of agents within the scope of the invention to a mammal having any of the recited cardiovascular indications.

Therefore, withdrawal of the 35 U.S.C. § 112 enablement rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 153-154, 158, 160-163, 174-176, and 181-184 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Barath et al. (U.S. Patent No. 5,242,397) and Thompson et al. (Br. J. Cancer, 63:609 (1991)) in view of Yang et al. (U.S. Patent No. 5,219,548). This rejection is respectfully traversed.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to administer a structural analog of tamoxifen to treat atherosclerosis because of the prior art teachings of Barath et el. and Yang et al., and because Thompson et al. teach methods ot measure TGF-beta levels and select agents that elevate TGF-beta levels.

Barath et al. disclose the local catheter delivery of PKC inhibitors, including tamoxifen, to prevent or inhibit restenosis after balloon angioplasty by preventing SMC proliferation. The catheter is designed to physically breach the vessel endothelium to deliver the PKC inhibitor into the interior of the vessel wall. At column 4, lines 46-49 of Barath et al. it is further disclosed that after angioplasty, smooth muscle cells proliferate in response to a number of factors, including growth factors, such as TGF.

There is no disclosure or suggestion in the Barath et al. patent of an agent that increases the level of TGF-beta, a growth factor. In fact, as employed by the Barath et al. patent, the PKC inhibitors inhibit growth factor transduction (column 4, lines 39-45), e.g., inhibit TGF-beta, thus effectively eliminating or reducing any biological effect induced by the growth factor. Thus, Barath et al. teach away from the use of a TGF-beta elevating agent to treat cardiovascular indications.

Thompson et al. and Yang et al. relate to the effect of agents on breast cancer cells or binding of tamoxigen analogs to the estrogen receptor on pig uteri. Thus, it is unclear to

Applicant how the disclosures in Thompson et al. and Yang et al. supplement the disclosure in Barath et al. There is nothing in the combination of Barath et al., Thompson et al. and Yang et al. that discloses the use of tamoxifen analogs or other agents that elevate TGF-beta to treat cardiovascular indications. And given the teachings in Barath et al., the combination of the cited art does not provide a reasonable expectation that TGF-beta elevating agents would be useful to treat cardiovascular indications.

Moreover, the Examiner is requested to reconsider that not all structural analogs of tamoxifen elevate TGB-beta (see the Rule 132 Declaration submitted on August 12, 2009). Thus, the combination of the cited art does not provide a reasonable expectation that any particular agent that is structurally related to a compound that elevates TGF-beta would likewise elevate TGF-beta and so be useful to treat similar, much less distinct, indications.

Therefore, withdrawal of the § 103(a) rejection of claims 153-154, 158, 160-163, 174-176, and 181-184 over Barath et al., Thompson et al. and Yang et al. is respectfully requested.

Claims 153-154, 158-163, 174-176, and 181-184 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Barath et al. and Thompson et al. in view of Knabbe (Am. J. Clin. Oncol. 1991, 14:S15) and Warri et al. (J. Natl. Cancer Inst. 1993, 85:1412). This rejection is respectfully traversed.

Barath et al. and Thompson et al. are discussed above.

Knabbe et al. report that that the *in vitro* addition of droloxifene, tamoxifen and toremifene to MCF-7 breast cancer cells induces TGF-beta.

Warri discloses that in breast cancer cells *in vitro*, toremifene increases TGFβ1 and promotes apoptosis.

Thus, Knabbe et al. and Warri do not supplement what is missing in Barath et al. and Thompson et al. discussed above.

Withdrawal of the rejection of claims 153-154, 158, 160-163, 174-176, and 181-184 under 35 U.S.C. § 103(a) over Barath et al., Thompson et al., Knabbe et al., and Warri is respectfully requested.

Claim 164 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Barath et al., Thompson et al., Knabbe et al., and Warri et al. and further in view of Cullinan et al. (U.S. Patent No. 5,457,113). Claim 164 is also rejected under 35 U.S.C. § 103(a) as being unpatentable over Barath et al., Thompson et al. and Yang et al. and further in view of Cullinan et al. These rejections are respectfully traversed.

Claim 164 depends on claims 153 and 154, which are believed to be patentable for the reasons discussed above. It is believed that the addition of Cullinan et al., which discloses coronary artery stents as pharmaceutical agent delivery devices, does not supplement the deficiency of the combination of Barath et al., Thompson et al., Knabbe et al., and Warri or the combination of Barath et al., Thompson et al. and Yang et al.

Thus, withdrawal of the rejections of claim 164 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date February 23, 2010

By /Janet Embretson/
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 23rd day of February, 2010.

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Name

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Signature